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Magnetic Nanocomposite Devices for Cancer Thermochemotherapy

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1. Introduction

The combination of nanotechnology and medicine has yielded a very promising offspring that is bound to bring remarkable advance in fighting cancers. In particular, nanocomposite materials based novel nanodevices with bi- or multi- clinical functions appeal more and more attention as such nanodevices could realize comprehensive treatment for cancers. Because it can provide an effective multimodality approach for fighting cancers, cancer comprehensive treatment has been fully acknowledged. Among the broad spectrum of nano-biomaterials under investigation for cancer comprehensive treatment, magnetic nanocomposite (MNC) materials have gained significant attention due to their unique features which not present in other materials. For instance, gene transfection, magnetic resonance imaging (MRI), drug delivery, and magnetic mediated hyperthermia can be effectively enhanced or realized by the use of magnetic nanoparticles (MNPs) (Shinkai 2004; Ito 2005). Therefore, MNPs are currently believed with the potential to revolutionize the current clinical diagnostic and therapeutic techniques.

In therapeutic oncology, nanothermotherapy is one of the effective approach based on MNPs, which can be achieved by applying nanoscaled metallic particles that convert electromagnetic energy into heat, for instance, magnetic fluid hyperthermia (MFH) mediated by superparamagnetic iron oxide nanoparticles (SPIONs) (Gazeau 2008). Upon exposure under alternative magnetic field (AMF), SPIONs can generate heat through oscillation of their magnetic moment (Figure 1).Currently, clinical trials at phase II are now under investigations for MFH on patients in Germany and Japan and demonstrate very inspiring for cancer therapy (Ito 2008). Except for nanothermotherapy, another possible and most promising application of MNPs is in drug delivery as carriers for chemotherapeutic agents for sustained or controlled delivery for cancer treatment. Compared with the organic materials including polymeric nanoparticles, liposomes and micelles under investigation as drug delivery nanovectors, the main advantages of MNPs as drug carriers summarized by

Manuel Arruebo can be: (i) visualized (SPIONs for MRI); (ii) guided by means of permanent magnetic field; and (iii) heated in a magnetic field to trigger drug release and/or combined with hyperthermia (Arruebo 2007). These advantages can help to yield an improved treatment efficacy and reduction of unwanted side effects. Moreover, it should be particular to point that the later capacity of MNPs is of special significance as the hallmarks of hyperthermia and its pleotropic effects are in favour of its combined use with chemotherapy (Issels, 2008). Therefore, hyperthermia and chemotherapy can be integrated into unique formulations or devices through smart engineered MNC materials, which enabling simultaneously thermochemotheray for cancer treatment. Herein, followed by a brief overview on nanothermotherapy and thermochemotherapy, we will review the design and fabrication strategies for the development of MNC devices for thermochemotherapy.

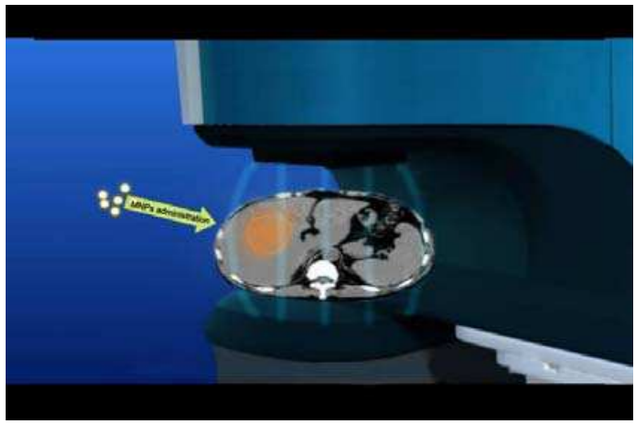

Fig. 1. Scheme of magnetic nanothermotherapy mediated by SPIONs

2. Magnetic nanothermotherapy

"*Quae medicamenta non sanat; ferrum sanat. Quae ferrum non sanat; ignis sanat. Huae vero ignis non sanat; insanabilia reportari oportet*" (Those diseases which medicines do not cure, the knife cures; those which the knife cannot cure, fire cures; and those which fire cannot cure, are to be reckoned wholly incurable).

- Hippocrates of Kos (*ca.* 460 BC – *ca.* 370 BC), Western father of medicine

From aphorism by Hippocrates, he believed that diseases could be cured by raising the patient's body temperature. Although the biological effectiveness of heat in treating cancer has been fully recognized for decades, and many of its molecular mechanisms are elucidated, however, in oncology clinical hyperthermia is currently regarded as the forth method of therapy after surgery, chemotherapy and radiotherapy (Hilderbrandt 2002). Technical challenges associated with the currently available hyperthermia modalities can explain the seemingly inconsistency, which may include: (i) the difficulty of the uniform heating only within the tumor region until the required temperature is reached while without damaging the normal tissues nearby, and (ii) the inability to create hyperthermia uniformly throughout the tumor volume (Saniei 2009). While the former may bring some unwanted side effect of the treatment or unnecessary harm to the patient, the later would leave defective cells unharmed, thus resulting in relapse of the tumor. Therefore, the development of novel hyperthermia technique capable of specifically targeting tumor tissue and cells is highly desired.

Application of nanotechnology has become central focus on cancer treatment and it also offers new opportunities and innovative solutions to hyperthermia. The marriage of nanotechnology and hyperthermia has yielded nanothermotherapy that is set to bring momentous advance in the fight against cancers. As mentioned above, this can be achieved by the design of nanometric heating-generating 'foci' which can be activated remotely by an external AMF (Gazeau 2008). As a completely new approach for targeted cancer treatment, nanothermotherapy couples the energy magnetically (through Brownian relaxation or Neel relaxation) to nanoparticles only within cancer tissue. In this way, nanothermotherapy aims at treating cancer from the cellular or intracellular level, as it is intended the design of nanostructured devices capable of penetrating selectively into cancer cells in order to generate lethal heating from the cell inside. This process can lead to direct killing of the local tumor tissue quickly, specifically and homogeneously, in the meanwhile, nanothermotherapy can also effectively activate the immune system to attack distant tumor site, a phenomenon known as abscopal effect in cancer treatment.

The external AMF applied in the treatment belongs to low or middle frequency electromagnetic (EM) field. Currently, EM radiation has been considered as a fundamental tool in cancer therapy, especially for diagnosis such as MRI and positron emission tomography (PET) as it is well accepted that EM fields are not especially contraindicated for humans (Goya 2008). The therapeutic potential of EM can be further explored in the magnetic nanothermotherapy and the magnetic field applicators at frequencies and field values are with full compliance to the safety regulations demanded in clinical applications. Safety demand is also the prerequisite criterion for MNPs therefore there is a multitude of known MNPs strongly restricted by the demand of non-toxicity and biocompatibility for the consideration of clinical applications. Normally investigations are focused on magnetic iron oxides Fe_3O_4(magnetite) and γ-Fe_2O_3(maghemite) which have been proved to be well tolerated by the humans.

Currently, the worldwide first magnetic nanothermotherapy against brain tumors, termed as Nano-Cancer® therapy is now under investigation in a phase-II study. Preliminary results show evidence of a local effectiveness and with only minor to moderate side effects. Besides the clinical trial, *In vitro* and animal experiments regarding MFH are widely carried out worldwide. Table 1 summarizes the major events associated with the development of magnetic nanothermotherapy.

3. Thermochemotherapy: thermal enhancement of drug cytotoxicity

In clinical, hyperthermia is usually applied as an adjunct treatment to an already established treatment modality such as chemotherapy, as hyperthermia can effectively enhance the cytotoxicity of various antineoplastic agents (thermal chemosensitization). In several clinical phase-III trials, an improvement of both local control and survival rates have been demonstrated by adding local/regional hyperthermia to chemotherapy in patients with locally advanced or recurrent superficial ad pelvic tumors. Additional application of selected chemotherapeutic drugs has been shown to enhance the inhibition of clonogenic cell growth at elevated temperatures both *in vitro* and in animal experiments. Thermal enhancement of drug cytotoxicity is accompanied by cellular death and necrosis without increasing its oncogenic potential. It also has been recognized that mechanisms for the thermal enhancement include increased rate constants of alkylation, increased drug uptake and inhibition of repair of drug-induced lethal or sub-lethal damage, etc. Generally,

Time	Milestone Events
1957	The concept of MMH was initially described by Gilchrist et al (Gilchrist 1957)
1959	MMH with magnetic particles was carried out on rabbits in which inguinal lymph modes were successfully targeted with heat (Medal 1959)
1979	The concept of intracellular hyperthermia was first proposed by Gondon et al (Gondon 1979)
1993	Jordan A et al published the first fundamental work describing the real potential of magnetic fluids for hyperthermia (Jordan 1993)
2003~2005	MagForce Nanotechnology AG carried out the phase I clinical trials of MFH in Germany (Hauff-Maier 2007; Johannsen 2007; Wust 2006)
2005	MagForce Nanotechnology AG initiated the Phase II clinical trials of MFH in Germany
2008	The concept of Nanothermotherapy was first proposed (Gazeau 2008)
2009	The first report of post-mortem neuropathological findings of GBM patients undergone MFH was reported (Landeghem 2009)
2009	Ethical discussion on MFH for brain cancer was published (Muller 2009)

Table 1. Major events associated with the development of MMH.

supported by a wealth of biomedical and molecular biological data, the results of clinical trials strengthen the current evidence that hyperthermia combined with chemotherapy is an effective and practical modality which should be integrated in the present cancer treatment armamentarium (Issels 2008).

4. Design, fabrication and evaluation of magnetic nanocomposite devices for thermochemotherapy

In recognition that MNPs can be acted simultaneously as mediators for magnetic nanothermotherapy as well as drug carriers, it is thus highly feasible to design and fabricate drug incorporated MNC devices for multimodal cancer treatment of thermochemotherapy, to realize the possible thermal enhancement to drug cytotoxicity. As MNPs comprise the ' scaffold ' of the nanocomposite devices, we will first address the protocols for the synthesis and surface modification of MNPs, and then design and fabrication strategies of the MNC devices will be described.

4.1 Synthesis and surface modification of MNPs

As mentioned above, iron oxide is the material under close investigation for medical application due to its superior biocompatibility with respect to other magnetic materials. Apart from biocompatibility, high magnetization, small size (less than 100nm), and narrow particle size distribution are also key factors for MNPs to be applied in nanothermatherapy. For this purpose, dozens of protocols for SPION synthesis have been developed in recent years, including co-precipitation, organic phase synthesis, solvothermal synthesis, etc. The simplest, cheapest and most environmentally-friendly procedure by far is based on the co-precipitation method, which involves the simultaneous precipitation of Fe^{2+} and Fe^{3+} in basic aqueous media.

Since the as-synthesized SPIONs in the colloidal form (known as ferrofluid or MF) have a large surface area to volume ratio, they are easily to undergo aggregation to form large

Fig. 2. TEM images of the Fe_3O_4 nanoparticles. a: surface modified with oleate sodium; b: un-modified nanoparticles

clusters. Therefore, surface coating or modification is required to improve the properties of the MF, such as stability and dispersity. Figure 2(a) illustrates the high-resolution transmission electron micrographs (TEM) of Fe_3O_4 nanoparticles. Due to the large specific surface area, high surface enery, and magnetization of the MNPs, the un-modified nanoparticles were severely aggregated (Figure 2(b)). However, after surface modification by sodium oleate, the nanoparticles are almost mono-dispersed with seldom aggregation. Stability of the MF can also be significantly enhanced and the MNPs are able to suspend in aqueous environment stably for months after surface modification. Besides, inductive heating capacity of MNPs, a vital issue related with nanothermotherapy can be greatly promoted by proper modification. Except for physical and chemical properties of the MNPs, endocytosis or cell uptake of the MNPs can be optimized and it has been reported that the aminosilan coated MNPs would be taken up by prostate carcinoma cells but not by normal prostate cells. All the findings strongly suggest surface modification plays critical roles in the properties of MNPs and therefore to this end, great attentions have been paid on choosing appropriate coating materials for functional modifications of SPIONs and detailed information can be referred to the careful reviews (Mornet 2004; Gupta 2005; MCCarthy 2008; Sun 2008).

4.2 Magnetic nano-drug by surface modification chemistry for cancer thermochemotherapy

In relation to the multi-therapy modality of thermochemotherapy, the intention for the design of nanocomposite devices is to use MNPs as one single tool for the combination of hyperthermia and chemotherapy to reach an enhanced therapeutic effect. So far there have been developed series protocols on how to engineer the two moieties within a single nanoplatform. Magnetic nano-drug by surface modification chemistry represents a kind of formulation to conjugate or attach drug molecules to the surface of MNPs. A number of physical or chemical approaches have been developed for the conjugation or attachment of functional molecules with MNPs surface which can be categorized into covalent linkage and physical interactions.

Physical interactions mainly include electrostatic, hydrophilic/hydrophobic and affinity interactions. For some charged drug molecules, electrostatic interactions have particularly useful in the assembly of magnetic nano-drugs, for instance, cisplatin-functionalized MNPs. Cisplatin belongs to platinum-based chemotherapy drug used to treat various types of cancers. It can form irreversible crosslink with bases in the DNA and ultimately triggers

apoptosis. It has been approved by US FDA for the treatment of a variety of malignancies including testicular, ovarian, bladder, small cell lung, as well as head and neck cancers. To fabricate cisplatin magnetic nano-drug, the SPIONs cores were coated by a soluble starch derivatives so that particles were negative charged with zeta potential of -41mv, allowing electrostatic binding of positively charged aquated cisplatin molecules (molecular structure shown in Figure 3). The binding process is rapid with high efficiencies. It was reported the prepared cisplatin magnetic nano-drug demonstrated ideal inductive heating property under AMF. A temperature increase of 47.3K was observed under AMF within 3 minutes, which is adequate for hyperthermia treatment (Kettering 2009). Besides, heating can also promote a rapid release of cisplatin from the MNPs. Babincova ever reported that under the influence of magnetic heating, almost all the drug could be released after 20min, in contrast to the spontaneous release of cisplatin that was only 20% after this time (Babincova 2008). This cisplatin release will be favorable for successful chemotherapeutic activity and should increase the therapeutic effect of magnetic heating treatment in medicinal application. *In vitro* cytotoxicity of the combined treatment by the cisplatin magnetic nano-drug has been carried out on the treatment of BP6 rat sarcoma cells and the results showed that the combination therapy is strongly synergistic.

Fig. 3. Molecular structure of Cisplatin (left) and aquated cisplatin (right)

Compared with physical interactions, a much broader spectrum of approaches have been developed based on the covalent linkage or chemical coupling strategy. In a most recent review paper, Veiseh et al summarized that covalent linkage mainly comprises three approaches: direct nanoparticle conjugation, click chemistry and covalent linker chemistry (Veiseh 2010). Unique advantages and drawbacks of each of the three approaches were addressed in detail. Here, we report the fabrication and characterization of epirubicin-immobilized magnetic nano-drug that may potentially be applied for thermochemotherapy.

Epirubicin (molecular structure shown in Figure 4) is an anthracycline drug used for chemotherapy, which acts by intercalating DNA strands. Intercalation results in complex formation which inhibits DNA and RNA synthesis. It also triggers DNA cleavage by topoisomerase II, resulting in mechanisms that lead to cell death. In order to immobilize the epirubicin molecules onto the surface of MNPs, conjugation strategy by linker chemistry was adopted. Briefly, polyarylic acid (PAA) was applied as the coating material to introduce carboxyl groups onto the SPIONs surface. The amino group of epirubicin can be conjugated with SPIONs via amide bond by applying the carbodiimides (EDC) and N-hydroxysuccinimide (NHS or sulfo-NHS) as the chemical linkers. The immobilization scheme of the conjugation was illustrated in Figure5.

Figure 6 demonstrates the shape, size and degree of uniformity of the PAA modified and epirubicin immobolized SPIONs. Both SPIONs are spherical in shape, mono-dispersed with diameter around 10nm. There is no significant change in size after epirubicin conjugation. X-ray powder diffraction patterns of epirubicin conjugated SPIONs was shown in Figure 7. From the pattern of the sample, it was found that there were a series of characteristic peaks at 2.968(220), 2.535(311), 2.103(400), 1.719(422), 1.614(511) and 1.478(440), demonstrating the

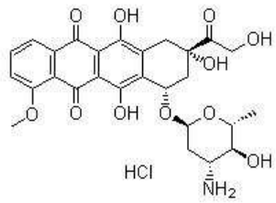

Fig. 4. Molecular structure of epirubicin

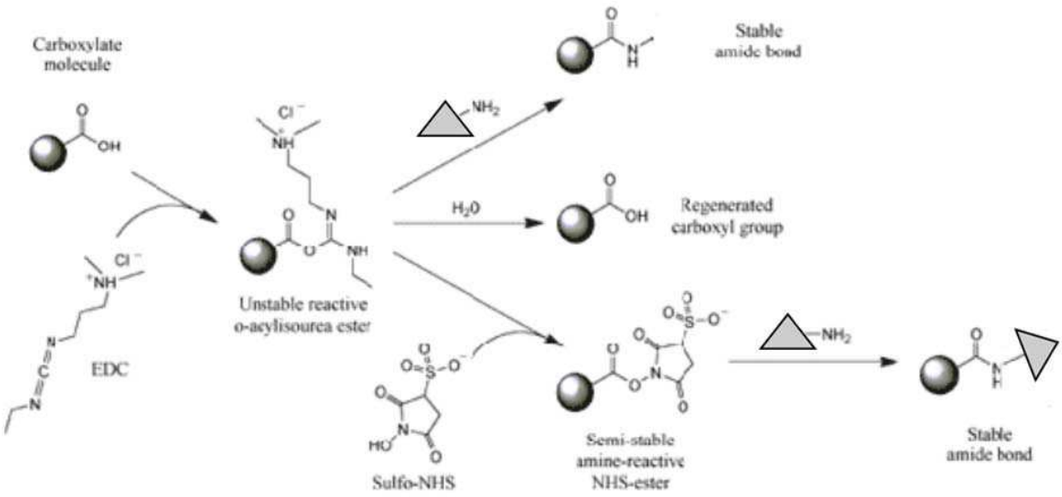

Fig. 5. Immobilization scheme of the conjugation of epirubicin and SPIONs by applying EDC/Sulfo-NHS as chemical linkers

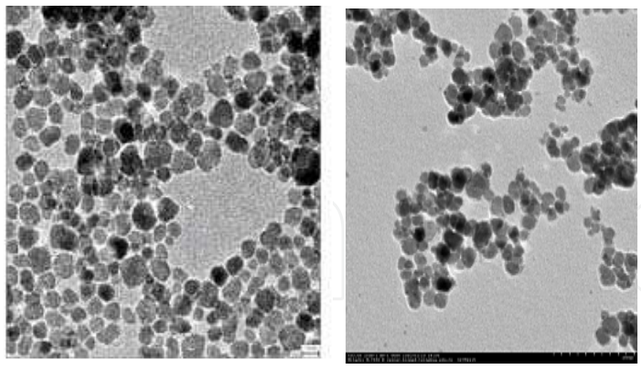

Fig. 6. Morphology of MNPs by TEM (left: PAA-MNPs; right: EPB-PAA-MNPs)

patterns were well indexed to the inverse cubic spinel phase of Fe_3O_4. This suggested that conjugation of epirubicin to the SPIONs has no effect on the crystalline structure of the SPIONs cores. The VSM measurement of magnetization of the epirubicin-MNPs at 300K is also shown in Figure 7. It can be seen from this figure that the MNPs show supermagnetic characteristics with zero hysteresis cycle. No coercive field and remnant magnetization can be observed. However, the magnetization was remarkably decreased by the conjugation of epirubicin onto the SPIONs.

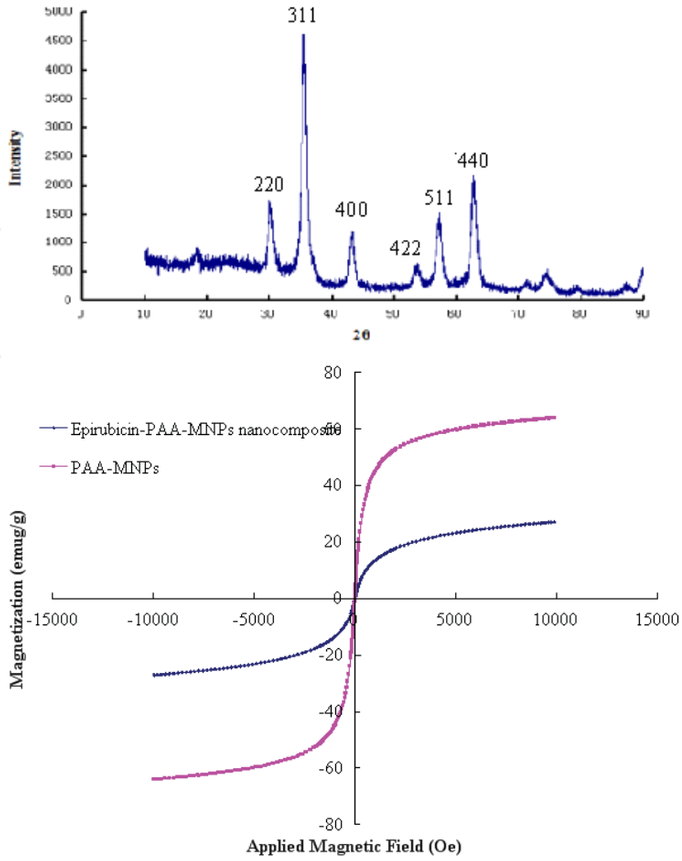

Fig. 7. XRD and magnetization curve of MNPs

The heating profiles of the epirubicin-MNPs suspensions with different MNPs concentrations under AMF of 300kHz were shown in Figure 8. As can be seen in Figure 8, higher particle concentration results in a greater increase in the temperature. The desired temperature can be achieved by appropriate adjusting the MNPs concentration.

Effect of heating on the epirubicin release was shown in Figure 9, which clearly demonstrated that under the influence of magnetic heating, almost all the drug can be released after 48 hour, in contrast to the spontaneous release of epirubicin that was only 50% after this time period. *In vitro* evaluation of the thermochemotherapy mediated by epirubicin-MNPs was carried out by the treatment of human gastric cancer SGC-7901.The viability data of SGC-7901 cells subjected to mono- treatment by epirubicinl and nanothermotherapy, as well as bi-modal treatment by thermochemotherapy are summarized in Figure 10. Assessment of viable SGC-7901 cells after various treatments showed mono-treatment treatment by hyperthermia or epirubicin released from magnetic nano-carrier could cause retarded proliferation on the cells. When the bi-modal treatment was applied on the cells, an even significantly greater decrease can be noticed on the cell viability ($p<0.05$), indicating an intensity effect of nanothermotherapy on epirubicin treatment. Although *in vivo* investigation should be carried out for the validation of the formulation, the findings we report here strongly support that drug conjugated MNC fabricated by covalent linkage is feasible for a combined thermochemotherapy in the cancer treatment.

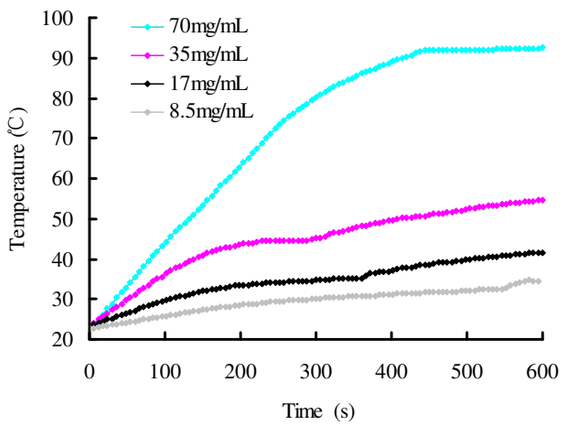

Fig. 8. Heating profiles of the epirubicin-MNPs suspensions with different MNPs concentrations under AMF of 300kHz

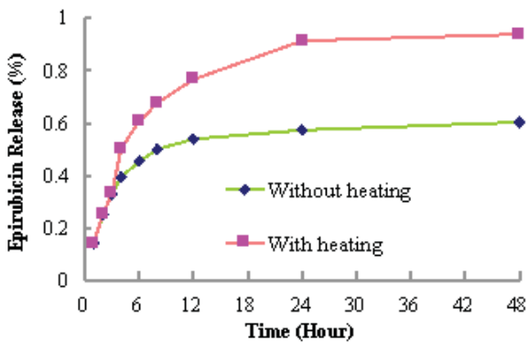

Fig. 9. Effect of heating on the epirubicin release from the EPB-MNPs

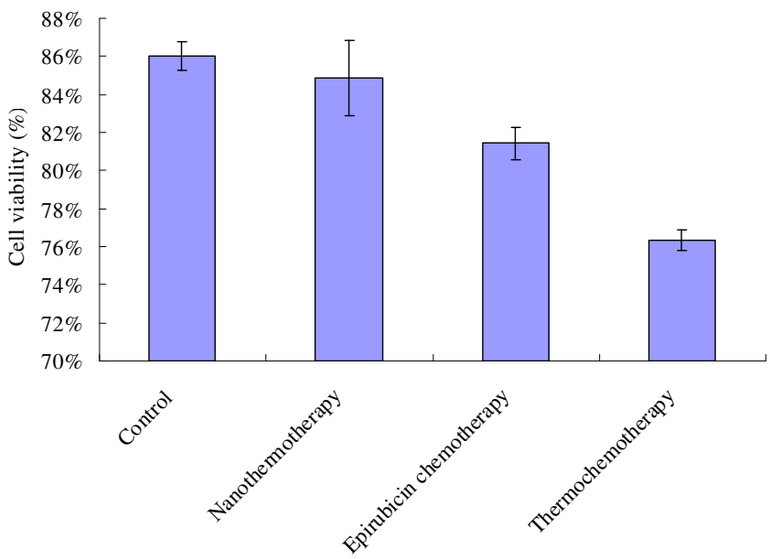

Fig. 10. Comparison of different treatment modality on the SGC-7901 cell viability

4.3 Solar-planet structured magnetic nanocomposite devices for cancer thermochemotherapy

Although surface modification chemistry provides a versatile tool for conjugating the drug molecules onto the MNPs surface, there is still some restrictions for this strategy. It was suggested by Veiseh et al that the choice of chemistry should be dictated by the chemical properties and functional groups found on the SPION coating and ligand to be linked (Veiseh 2010). For most of the drug molecules, there are no proper functional groups nor is it convenient to introduce such a functional group onto the MNPs surface for further conjugation. Besides, SPIONs applied in nanothermotherapy are normally hydrophilic, whilst there are numerous drugs are not soluble in water, therefore it is very challenging to find an appropriate medium to carry out the modification chemistry. We thus report here so-called solar-planet structured MNC devices for the combined thermochemotherapy. In the present study, docetaxel is used as a model small molecule anticancer drug, which is a poorly water-soluble, semi-synthetic taxane analog commonly used in the treatment of breast cancer,ovarian cancer, small and non-small cell lung cancer, prostate cancer. For the purpose of fabricating the solar-planet structured MNC devices, docetaxel loaded polymeric nanoparticles (DNPs) composed of carboxylic-terminated poly(D,L-lactic-co-glycolic acid) (PLGA) with Vitamin E TPGS as emulsifier for sustained drug release were prepared by a modified solvent extraction/evaporation technique. Intensive investigations have been carried out for the DNPs and the detailed fabrication protocols of DNPs could be found from the published work (Feng 2007). The size of the DNPs fabricated by solvent evaporation method is around 200nm. Furthermore, the MNPs modified with amino groups could be covalently attached to the surface of carboxylic terminated DNPs to form the so-called solar (DNPs)-planet (MNPs) structured MNC by EDC/NHS crosslinking protocol as illustrated in Figure 5.

TPGS-emulsified PLGA nanoparticles were found more advantageous than any other kind of PLGA nanoparticles in resulting much higher drug EE, cellular uptake, and *in vitro* cancer cell cytotoxicity, and more desirable *in vivo* pharmacokinetics. The nanoparticles were found to be spherical with diameter of 200nm (Figure 11), which are close to the optimum size for cellular uptake *in vitro*. Before carrying out *in vitro* and *in vivo* investigations on the novel nanocomposite for thermochemotherapy, fluorescent observation was applied to confirm the formation of the solar-planet structured MNC. Firstly, docetaxel loaded PLGA NPs were labelled with coumarin-6 as the fluorescent marker. After the conjugation of the amino-coated MNPs and the fluorescent PLGA NPs, the product was collected by the permanent magnet and then underwent thorough washing for at least 3 times by DI water. The suspension was then subjected for fluorescent observation. It is clearly demonstrated from Figure 12 that there is much stronger fluorescent intensity compared with the control group, where there was no the linker molecules EDC/NHS during the conjugation. This observation strongly confirmed the formation of the so-called solar-planet structured MNC.

Our *in vitro* analysis has demonstrated the thermal enhancement on docetaxel cytotoxicity can be achieved by the solar-planet structure MNC (data not shown). Further on, this novel nanocomposite device was applied *in vivo* to evaluate the effect of themochemotherapy on the tumor bearing nude mice. The temperature for hyperthermia was controlled around 46°C and the drug was administered at 10mg/kg dose. The time course of C6 tumor nodules growth subjected to different treatment was shown in Figure 13, which is obviously demonstrated that the tumor volume of the mice in the control group steadily increased with no evidence of regression. While both mono-treatment of thermotherapy and

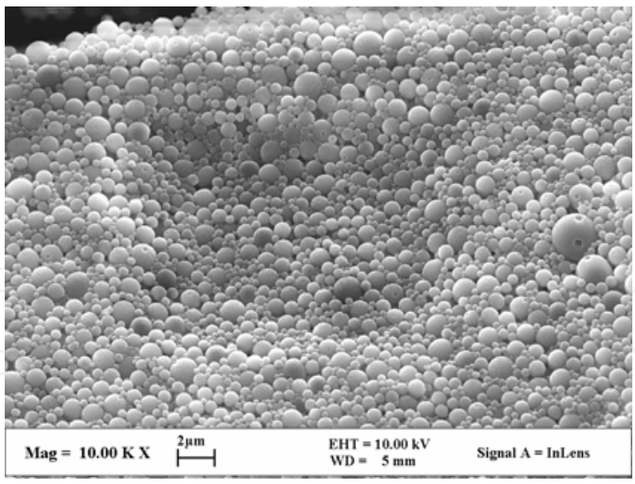

Fig. 11. SEM images of docetaxel loaded polymeric nanoparticles

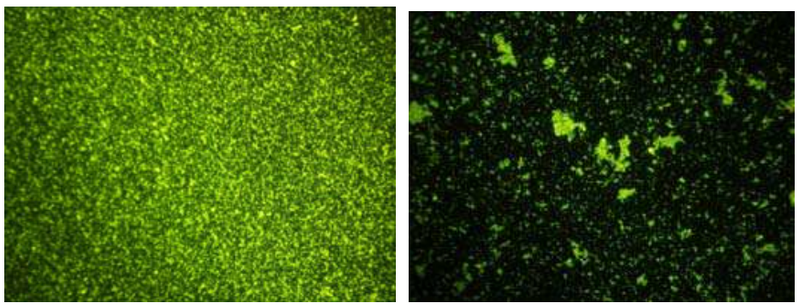

Fig. 12. Fluorescent observation of conjugation MNPs with DNPs by covalent linker chemistry with (left) and without (right) the application of EDC/NHS as chemical linkers.

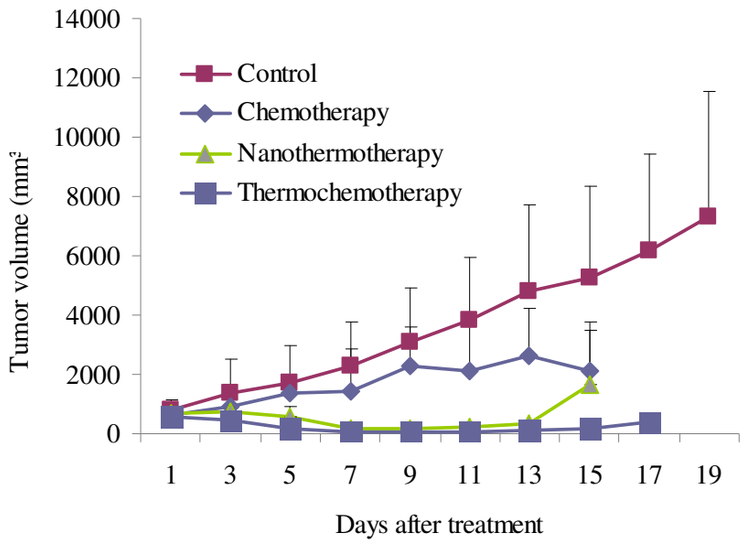

Fig. 13. Tumor growth of C6 cells in non-treated control mice (n = 10), mice treated with nanothermotherapy (n = 10, T=46℃), mice treated with docetaxel (dose=10mg/kg) and mice treated with themochemotherapy. Points, mean tumor volume (mm^3); bars, SD.

chemotherapy can greatly inhibit the *in vivo* tumor growth, tumor volume in the group of bi-modal treatment mediated by the novel MNC was significantly reduced compared with chemotherapy ($p<0.05$) and control group ($p<0.001$). Our observation supports that solar-planet structured MNC is a novel and effective mediator for magnetic thermochemotherapy. The MNC can realize cancer comprehensive treatment thus has great potential in clinical application.

4.4 Drug loaded magnetic nanocomposite biodegradable implants for cancer thermochemotherapy

Either the magnetic nano-drug or the solar-planet nanocomposite discussed above is in the injectable formulation. The particles are dispersed in the aqueous continuous phase (most often PBS buffer) to form a stable nanocomposite colloid or suspension. For clinical application, the colloid or suspension can be administered by direct injection, arterial infusion or intravenous infusion. However, in some cases the injectable formulations may result in limited clinical effectiveness, for instance, post-surgical local cancer treatment for malignant gliomas. Malignant gliomas such as glioblastoma multiform (GBM) characterized by aggressive proliferation of undifferentiated cells, pervasive invasion into distant healthy brain tissue and a high penchant to recur is among the most recalcitrant tumors to be treated. Currently, surgical debulking of the accessible tumor from the patient's brain is the conventional clinical treatment for glioma. However, the amount of tumor removed is often limited by proximity to critical regions for brain function, thus resulting in risk of tumor re-growth from residual tumor. In clinical, cancer remission can be limited by conventional systemic post-surgical treatment and for this purpose, biodegradable controlled release polymeric implants could be surgically located at the site of tumor removal during the debulking surgery.

It is well acknowledge that the use of surgically implanted local release systems made of biodegradable polymers for drug delivery over extended periods of time has good potential in glioma treatment. Gliadel® (polifeprosan 20 with carmustine implant) has been approved by the US FDA for use in post-surgical local chemotherapy against recurrent malignant glioma. However, despite its potential, clinical trials with commercial Gliadel® wafer delivering carmustin vs. Placebo wafers have been shown to small improvements in median survivability of patients diagnosed with high-grade malignant gliomas from 11.6 to 13.9 months, and from 4.6 to 6.4 months for recurrent cases. In response, Ranganath et al have explored the controlled release of alternative chemotherapeutic agents (paclitaxel) and fadiosensitization (etanidazole) for treatment (Ranganath 2010). Since the advantages for comprehensive cancer treatment has been recognized, it is thus highly significant to develop composite polymeric surgical implant to achieve multimodality approach for fighting cancers. In principle, such kind of treatment can be realized by applying of the tailored magnetic nanoparticles (MNPs) composite polymeric film. Fe_3O_4 MNPs acting as the agent for MMH, and anti-cancer drug docetaxel as chemotherapeutic agent were incorporated within the biodegradable polymeric film (Zhao 2009).

Figure 14 gives the observations of the MNC film prepared by the solvent evaporation method. Poly (D, L) lactide-trimethylene carbonate (PLA-PTMC) copolymer was employed as the film matrix, as its inhibitive effect of adhesion formation after surgery has been confirmed. The film is flexible, smooth and homogeneous. Figure 2 also indicated a

morphology difference between the nanocomposite film surfaces of air-solvent interface and solvent-substrate interface. With the evaporation of the solvent and under the action of gravity, the MNPs would be precipitated out and deposited onto the substrate forming a rather rigid and homogeneous surface. On the other side, with a higher solubility with solvent, PLA-PTMC tends to concentrate at the air-solvent interface and formed an immiscible blending/mixture with MNPs clusters, which result in the roughness formation. It is worth mentioning that such a rough surface would be more significant for facilitating drug release from the polymeric matrix. The heating profiles of the nanocomposite polymeric films with different MNPs contents under AMF of 300kHz were shown in Figure 15. It is obvious to notice that the heating curve exhibits an asymptote, which signals the equilibrium of the heating process. The curves show the final temperatures upon equilibrium (Te) depend strongly on the MNPs contents, i.e. higher magnetic particles content within the film can ensure a higher Te. Another decisive factor for the heating process is the magnetic field intensity. As can be seen in Figure 15, higher field intensity

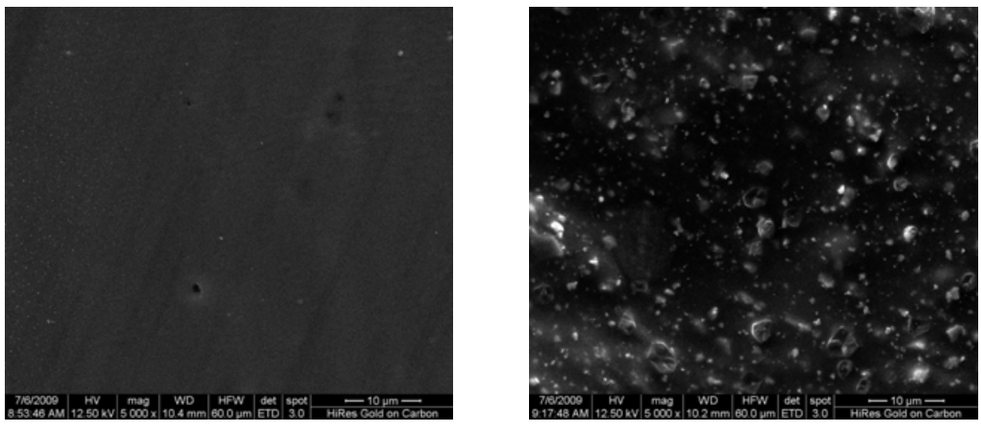

Fig. 14. SEM images of nanocomposite films (left: MNPs nanocomposite film(50% MNPs loading and 5%docetaxel loading) at solvent-substrate interface; right: same nanocomposite film at air-solvent interface)

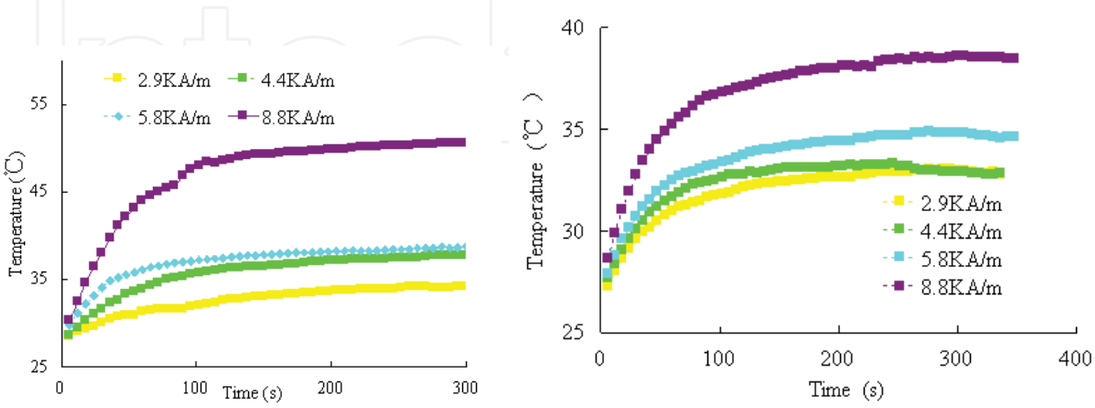

Fig. 15. Inductive heating profiles of nanocomposite films under AMF at different field intensity (left: with 50% MNPs; right: with 25% MNPs)

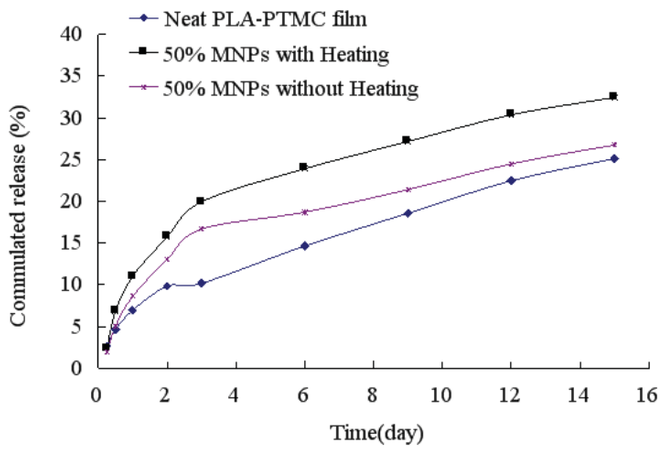

Fig. 16. *In vitro* drug release profile of docetaxel (5% drug loading)

results in a greater increase in the temperature, which means more energy can be generated by the MNPs within the films. The desired temperature can be achieved by appropriate choosing the MNPs content or adjusting the field intensity. All of these can guarantee the temperature requirement for the hyperthermia for cancer treatment. The release profiles of docetaxel from the polymeric films in 14 days were investigated and the results are shown in Figure 16. In general, the release of docetaxel from the films was characterized by an initial rapid release phase followed by a slower release phase. Figure 16 also demonstrates 20min exposure of the film under AMF would greatly facilitate the docetaxel release from the film. This phenomenon may be attributed to the accelerated diffusion of docetaxel from the film to the PBS buffer upon heating generated from AMF exposure.

Both *in vitro* and *in vivo* studies have been carried out for the evaluation of the biocompatability, cytotoxicity and anti-cancer effectiveness of themochemotherapy mediated by the MNC film. Biocompatability of the prepared nanocomposite film has been fully confirmed by *in vitro* and *in vivo* investigations. Assessment of viable C6 cells after various treatments showed treatment by docetaxel released from film could cause retarded proliferation on the cells. When the bi-modal treatment by combination of MIH and chemotherapy was applied on the C6 cells, an even significantly greater decrease can be noticed on the cell viability ($p<0.01$, data not shown), indicating an intensity effect of MIH on docetaxel treatment. The *in vivo* study was performed tumor bearing nude mice. Xenografts of human glioma cell lines would be established by subcutaneous inoculation of U251 MG cells into the hind legs of BALB/c nude mice. For animals under placebo and experimental groups, a small incision by aseptic surgery was performed on the skin and tumor was reached after which 3/4 tumor volume would be carefully excised. The film discs would then be implanted well onto the residual tumor bed and subsequently the wound would be closed using subcutaneous suturing. Mice were then exposed under the AMF for 30mins treatment and the temperature of the tumor site was about 46°C. The body temperature was not affected and the mice did not have symptoms of dehydration and all survived the whole experiment of two weeks. Tumors in the thermochemotherapy group shrunk most significantly, as compared with those of the control groups and hyperthermia treatment only.

Fig. 17. The clinical photography of the tumor of mice under different treatment after 10 days (left: control; middle: hyperthermia (46°C) only and right: Thermochemotherapy by the nanocomposite film (46°C, docetaxel dose=10mg/kg).

5. Conclusion

In this chapter, various MNC devices for cancer thermochemotherapy are discussed and the detailed structures are summarized and illustrated in Figure 18. Except for the above-mentioned MNC devices, drug encapsulated magnetic cationic liposome (MCL) and thermoresponsive core-shell MNPs are also under intensive investigation for the bi-modal therapy of combined hyperthermia with chemotherapy (Shinkai 2004; Purushotham 2010). The nanocomposite devices exhibit advantageous feature for a facilitated drug delivery from the nano-carriers and the magnetic mediated heating potential is adequate for hyperthermic treatments. We thus conclude that even though further detailed investigations are still necessary, tentative use in local tumor therapies aiming at a specific chemotherapeutic release in combination with magnetic heating is promising and feasible in the long term.

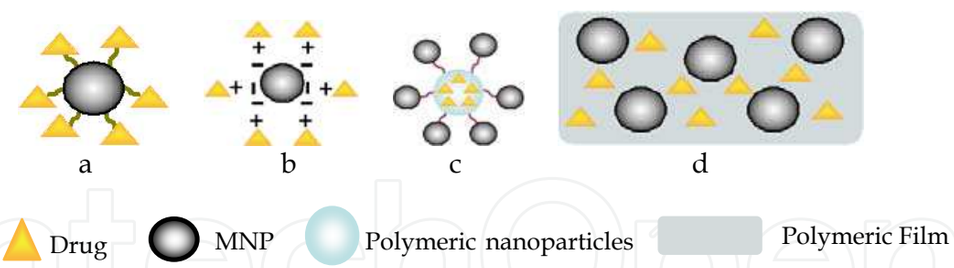

Fig. 18. Illustration of various MNC devices discussed in this chapter (a: Magnetic Nano-Drug by covalent linkage; b: Magnetic Nano-Drug by electrostatic interaction; c: solar-planet structured MNC; d: drug-loaded MNC film)

It is worth noting for the research and development on MNC devices for cancer thermochemotherapy discussed in this chapter, we only focus on the functions of MNPs as drug delivery carriers and mediators for MFH. Other features of MNPs, such as MRI contrast agent, gene transfection carriers as well as passive targeting driven by permanent magnet are not addressed here. Decisive understanding of the properties of MNPs will increase their potentials for medical applications, and the potentials of MNPs as unique platform for cancer diagnosis (MRI), nanothermotherapy, chemotherapy as well as gene therapy should be further explored to improve the medical techniques for cancer treatment.

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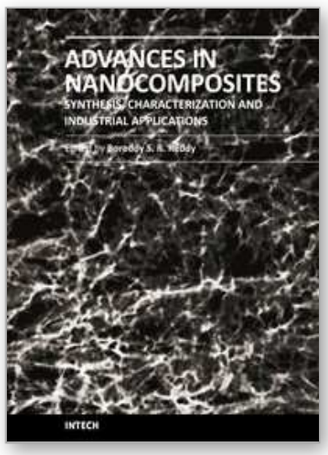

Advances in Nanocomposites - Synthesis, Characterization and Industrial Applications

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Advances in Nanocomposites - Synthesis, Characterization and Industrial Applications was conceived as a comprehensive reference volume on various aspects of functional nanocomposites for engineering technologies. The term functional nanocomposites signifies a wide area of polymer/material science and engineering, involving the design, synthesis and study of nanocomposites of increasing structural sophistication and complexity useful for a wide range of chemical, physicochemical and biological/biomedical processes. "Emerging technologies" are also broadly understood to include new technological developments, beginning at the forefront of conventional industrial practices and extending into anticipated and speculative industries of the future. The scope of the present book on nanocomposites and applications extends far beyond emerging technologies. This book presents 40 chapters organized in four parts systematically providing a wealth of new ideas in design, synthesis and study of sophisticated nanocomposite structures.

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